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Role of Sleep Deprivation in Fear Conditioning and Extinction: Implications for Treatment of PTSD

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14. ABSTRACT
PTSD is a growing concern for both active duty personnel and Veterans. Fear conditioning is implicated in the development of PTSD, while successful acquisition, consolidation, and recall of extinction memory are implicated in both the natural reduction of initial PTSD symptoms and as the mechanism underlying the most successful treatment for PTSD, Prolonged Exposure. In animal models, sleep deprivation has been shown to impair extinction memory, although this has never been directly tested in humans. This project is the first to examine the role of sleep and sleep loss in acquisition, consolidation, and generalization of extinction memory in humans.

15. SUBJECT TERMS
PTSD, sleep deprivation, fear conditioning, extinction memory, humans

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Introduction

PTSD is a growing concern for both active duty personnel and Veterans. Fear conditioning is implicated in the development of PTSD, while successful acquisition, consolidation, and recall of extinction memory are implicated in both the natural reduction of initial PTSD symptoms and as the mechanism underlying the most successful treatment for PTSD, Prolonged Exposure. In animal models, sleep deprivation has been shown to impair extinction memory. Indirect evidence in humans also supports that notion, but it has never been tested directly in humans. Some of the most ubiquitous and distressing symptoms of PTSD are insomnia and nightmares. The resultant sleep deprivation may actually serve to perpetuate the disorder by interfering with treatments designed to promote extinction memories. Before this hypothesis can be tested in clinical populations, however, well-controlled experimental studies need to establish the exact role of sleep deprivation in extinction acquisition, consolidation, and recall in humans. This study will do just that. This is a mixed-effects study designed to examine the impact of 36 hours TSD on fear conditioning and consolidation (Aim 1), as well as extinction memory acquisition, recall, and generalization (Aim 2). A total of 60 subjects will participate across 3 years. Following recruitment and screening, subjects will spend 4 nights and days in the laboratory: a) adaptation to the lab (Night/Day0); b) normal sleep followed by fear memory acquisition (Night/Day1); c) sleep or TSD followed by fear recall and extinction memory acquisition (Night/Day2); and d) sleep or TSD followed by a test of extinction recall and generalization (Night/Day3). Group1 will receive sleep prior to each testing day, Group2 will be sleep deprived prior to Day2, and Group3 will be sleep deprived prior to Day3.

Body

This report covers the third year of the project. All milestones as set out in the Statement of Work (SOW) were successfully met. The goals of the third year were to complete enrollment of subjects, analyze the data, and submit manuscripts for publication.

We have now completed enrollment of subjects, but this took longer than we anticipated. This was due largely to an unusually high proportion of subjects in the last year who were deemed ineligible after signing informed consent. The majority of these subjects did not show an appropriate startle response during the initial screening appointment, and thus we were unable run them through the full protocol. The result was several missed weeks of data collection and a delay in completing our targeted sample size. We have been granted a no cost extension on the study, which will afford us the time and resources to complete data process, as well as analyze data and submit papers for publication.

The numbers related to final subject enrollment are as follows. We conducted initial phone screens on 895 individuals. Of those, 126 preliminarily qualified based on the phone screen, were able to make the time commitment required for the study, and were subsequently enrolled through signing informed consent. Of those 126, 73 subjects completed the study. Of those not completing the study, 20 were excluded during the in-person intake due to being a non-responder to the startle paradigm, 6 were excluded during the in-person intake due to proving ineligible based on other criteria, 19 withdrew for personal reasons, 6 were dropped due to revealing information after the initial intake making them ineligible, and 2 were withdrawn for protocol violations. Thirteen (13) subjects completed the study but had sufficient artifacts in their startle data that the data is not usable. Thus, in total, we have 60 subjects with a full set of usable data. Our subjects with full data have included good diversity, with 24 women and 36 men, 16 Hispanic subjects, and 25 racial minorities (17 Asian, 1 Black, and 7 Mixed).

We have also remained largely up-to-date with all data processing, scoring, and archiving. Our current task is to finish this process prior to analyzing the data for the main study Aims.

Nonetheless, we have conducted an analysis for a secondary aim and are currently writing a manuscript for publication from those data (see Reportable Outcomes, below).

Key Research Accomplishments

Enrolled 126 subjects into the study, with 60 subjects who completed and provided fully usable data.

Reportable Outcomes

We have conducted analyses from one paper, thus far. While this paper is not part of the main Aims of the study, we believe it has the potential to make a strong contribution to the literature. A draft abstract is below.

Posttraumatic Stress Disorder (PTSD) is a common sequale of service in Operations Iraqi Freedom, Enduring Freedom, and New Dawn. Fear conditioning has proven an important animal model of PTSD, in part because patients with PTSD show impaired fear processes. A less known utility of the model is the impact on sleep. In animals, fear conditioning disrupts sleep, especially REM sleep. Sleep deprivation, in whole or just of REM sleep, in turn interferes with extinction of fear. Given the ubiquitous nature of sleep disruption in PTSD, there is growing interest in whether sleep plays a role in the impaired fear processes seen in PTSD. The aim of this study is to provide a translational test of the impact of fear conditioning, and its counterpoint safety learning, on sleep in humans. Subjects were 42 healthy young adults (age 24.2 ± 5.0 years, 40% female, 36% minority). After a week of regularized sleep at home, subjects slept in the laboratory for 3 nights. On the day following night 2, they underwent a startle paradigm where they learned threat (fear conditioning) and safety (safety learning) signals. On the day following night 3, fear and safety retention was tested. We examined the effects of initial learning on REM sleep and whether REM sleep subsequent to learning facilitated memory consolidation of threat and safety. Results showed increased safety learning was associated with increased consolidation of REM sleep the subsequent night. Increased consolidation of REM sleep predicted increased next-day retention of fear and safety learning, as well increased ability to discriminate threat from safety signals. These data represent the first human translation of animal models showing an impact of initial fear/safety learning on sleep and suggest a role for REM sleep in the ability to discriminate threat from safety. The findings have implications for PTSD, especially given REM sleep is characteristically disrupted in PTSD, as is the ability to differentiate threatening environments from safe environments.

Conclusion

We successfully enrolled our targeted sample in the study, and we are finishing data process for the main aims of the study. Our initial analysis of a secondary aim shows novel results with direct implications for PTSD. We anticipate submitting this manuscript, as well as 1-2 others, during the No Cost Extension period.

References

N/A

Appendices

Updated Quad Chart, showing figures from Outcome reported above

Supporting Data

N/A

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Study Aim

- Overall: Provide first translation study of impact of sleep deprivation on fear conditioning and extinction memory in humans
- Specific Aim 1: Determine if total sleep deprivation (SD) alters consolidation of fear conditioning
- Specific Aim 2: Determine if total SD impairs extinction memory acquisition, recall, or generalization

Approach: Between subjects study comparing normal night of sleep to 26 hours total SD wrt impact on fear conditioning, and extinction acquisition, recall, and generalization. Subjects are healthy human controls.

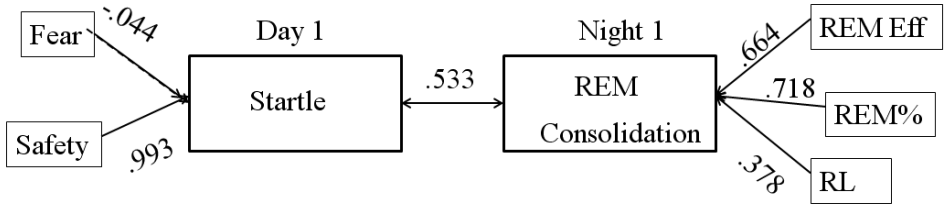

Fig 1: Model showing impact of startle paradigm on subsequent REM sleep

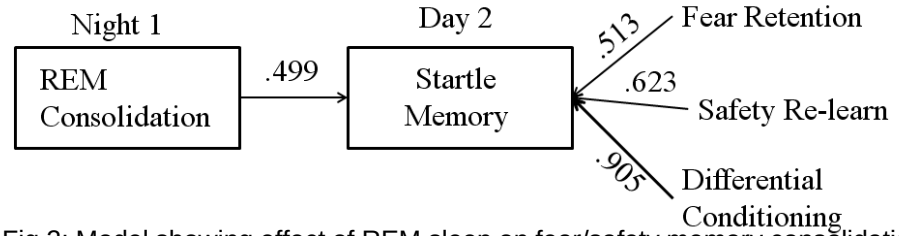

Fig 2: Model showing effect of REM sleep on fear/safety memory consolidation

Timeline and Cost

Activities	FY 11	FY12	FY13
***Task 1**: Regulatory Approval*			
***Task 2**: Hire and train*			
***Task 3**: Enrollment*			
***3a**: Enroll 14 subjects*			
***3b**: Cumulative enrollment of 53*			
***3c**: Cumulative enrollment of 72*			
***Task 4**: Analyze data & submit publication*			

Updated: 22 Oct 2013

Goals/Milestones

FY 11 Goals

☑ Regulatory approval
☑ Hire and train staff
☑ Enroll 14 subjects

FY 12 Goals

☑ Cumulative Enrollment of 53 subjects

FY13 Goals

☑ Cumulative enrollment of 72 subjects
☐ Analyze data and submit manuscripts